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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/637,530

Applicant(s)

STANNERS ET AL.

Examiner

Stephen L. Rawlings, Ph.D.

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 25-30 is/are pending in the application.
- 4a) Of the above claim(s) 26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25 and 28-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 26 and 27 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. The election with traverse filed April 2, 2004 is acknowledged and has been entered. Applicant has elected Group XXIII, claim 25, insofar as the claim is drawn to a method for relieving a CEA/NCA-imposed inhibition of differentiation and/or apoptosis comprising an incubation of primary or secondary tumor cells with an agent that disrupts an interaction involving a CEA/NCA subdomain having SEQ ID NO: 1.
2. The amendment filed April 2, 2004 is acknowledged and has been entered. Claims 12-24 have been canceled. Claim 25 has been amended. Claims 26-30 have been added.
3. Claims 25-30 are pending in the application. Claims 26 and 27 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed April 2, 2004.
4. Claims 25 and 28-30, insofar as the claims are drawn to the elected invention, are currently under prosecution.

### ***Election/Restrictions***

5. Newly submitted claim 26 and 27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 26 and 27 are drawn to a method for relieving a CEA/NCA-imposed inhibition of differentiation, and/or CEA/NCA-induced apoptosis, and/or CEA/NCA-imposed distortion of tissue architecture comprising an incubation of primary or secondary tumor cells with an anti-CEA/NCA antibody that disrupts a CEA/NCA interaction involving an interaction of amino acids at positions 30 to 82 of SEQ ID NO: 5 or involving an interaction of amino acids at positions 30 to 46 of SEQ ID NO: 5, respectively, whereas the elected invention is a method for relieving a CEA/NCA-

Art Unit: 1642

imposed inhibition of differentiation and/or apoptosis comprising an incubation of primary or secondary tumor cells with an agent that disrupts an interaction involving a CEA/NCA subdomain having SEQ ID NO: 1, i.e., amino acids 30 to 35 of SEQ ID NO: 5. Accordingly, the subject matter of the elected invention and the subject matter of claims 26 and 27 differ in that the agent or antibody interrupts an interaction of different subdomains of CEA/NCA comprising distinct amino acid sequences. Therefore, the search required to examine the elected invention is different from the search that would be required to examine the subject matter encompassed by either claim 26 or claim 27.

Since Applicant has received an action on the originally presented claims in the Office action mailed October 2, 2003 and in reply, elected an invention in the paper filed April 2, 2004, the subject matter of the instant claims that pertains to the subject matter of the elected invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 26 and 27 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. In the paper filed April 2, 2004, Applicant has traversed the restriction and election requirement set forth in the Office action mailed October 2, 2003. Applicant has argued the restriction is improper because the inventions are closely related and can be searched and examined together without serious burden, as evidenced by the fact that the elected invention and the inventions in groups XXIV and XXV have been classified identically.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

Although the inventions are related, the groups of inventions are distinct for the reasons set forth in the Office action mailed October 2, 2003. The search required for examination of any one of the groups of inventions is not coextensive with that that would be required to examine any other; and thus examination of each group of inventions requires a unique and different search. Consequently, searching more than one group of inventions would necessitate more than one search and would therefore

constitute a serious burden. MPEP § 803 states restriction is proper, where the groups of inventions are unrelated or distinct and searching the entire application would constitute a serious burden.

Therefore, the restriction and election requirement is deemed proper and is made FINAL.

### ***Drawings***

7. Receipt of the proposed change to the drawing filed November 5, 2002 is acknowledged. These proposed change to the drawing is acceptable. Applicant should submit a replacement drawing in which the proposed changes have been made.

### ***Information Disclosure Statement***

8. The information disclosures filed July 18, 2001 and November 5, 2002 have been considered. An initialed copy of each is attached hereto.

### ***Oath/Declaration***

9. The declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The declaration is defective because non-initialed and non-dated changes have been made.

### ***Priority***

10. Applicant's claim for domestic priority is acknowledged. However, the earlier applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for claims of this application for the reasons set forth below. Accordingly, the effective filing date of the claims is the filing date of the instant application, namely August 11, 2000.

In addition, it is noted that Applicant has not filed a certified copy of the Canadian patent application to which Applicant claims priority, as required by 35 U.S.C. 119(b).

***Response to Amendment***

11. The amendment filed August 15, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 26, and SEQ ID NO: 27 of the sequence listing filed August 15, 2003 find no support in the specification, as originally filed, since the specification does not describe peptides or amino acid sequences consisting of any of SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 26, or SEQ ID NO: 27.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Specification***

12. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., <sup>TM</sup>, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

13. The disclosure is objected to because of the following informalities:

- (a) "Overexpression" is misspelled as "everexpression" at page 8 (line 5); and
- (b) "Non-malignant" is misspelled as "non-malignat" at page 7 (lines 25).

Appropriate correction is required.

14. The specification is objected to because sequences appearing in the specification and/or drawings are not properly identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). In particular, there are amino acid sequences of 4 or more amino acids that are not properly identified in Figure 9. In addition, there are amino acid sequences of 4 or more amino acids, which are not properly identified, in the specification at page 5 (line 2), page 6 (lines 3 and 4), page 15 (lines 7, 10, 11, and 20), and page 16 (lines 8, 16, and 25). Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers.

#### ***Claim Objections***

15. Claims 25 and 28-30 are objected to because the claims are drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 112***

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 25 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new matter rejection.

Claim 25 recites, "CEA/NCA-imposed apoptosis". At page 4 of the amendment filed April 2, 2004, Applicant states support for the amended claim can be found in the

Art Unit: 1642

specification at page 8 (lines 23-25), page 13 (lines 20-33), and page 14 (lines 3-8 and 11-14). However, the specification defines "anoikis" as "apoptosis of anchorage-free cells" (page 2, line 31). Consequently, it does not appear that the originally filed specification provides proper and sufficient written support for the broader breadth of the present claim language, while it would provide written support for the narrower term, "CEA/NCA-imposed *anoikis*" in the context of the present claims.

Claim 25 recites, "primary" and "secondary". Applicant added claim 25 by the amendment filed August 11, 2000 without stating wherein the specification, including the claims, as originally filed, written support for the claim language can be found. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims". See MPEP § 714.02 and § 2163.06. Nevertheless, as MPEP § 2163 further states: "The examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. See *Wertheim*, 541 F.2d at 263, 191 USPQ at 97". It does not appear that the originally filed specification, including the claims, provides written support for the recitation of either term in the instant claim, because the description of a genus, i.e., a tumor, does not suffice to describe a species contained within the genus, i.e., a primary tumor or a secondary tumor.

Claim 25 recites, "which disrupts a CEA/NCA interaction involving a N-terminal domain of CEA/NCA". Applicant added claim 25 by the amendment filed August 11, 2000 without stating wherein the specification, including the claims, as originally filed, written support for the claim language can be found, but at page 4 of the amendment filed April 2, 2004, Applicant states support for the amended claim can be found in the specification at page 8 (lines 23-25), page 13 (lines 20-33), and page 14 (lines 3-8 and 11-14). Even so, it does not appear that the originally filed specification provides proper and sufficient written support for present claim language and moreover it does not appear to provide adequate written support for the breadth of that language. Notably claim 25, as originally presented, was interpreted to be drawn to a method for relieving a CEA/NCA-imposed inhibition of differentiation and/or apoptosis comprising an

incubation of primary or secondary tumor cells with an agent that disrupts an interaction involving a CEA/NCA subdomain and integrins  $\alpha_5\beta_1$  and  $\alpha_v\beta_3$ . Of narrower scope than the instant claim, it appears that the originally presented claim would not find adequate written support in the specification, including the claims, as originally filed, since it does not appear that the specification describes an inhibition by an agent of an interaction between the CEA/NCA subdomain of SEQ ID NO: 1 and such an integrin. At page 7 (lines 8-19), the specification describes anti-CEA/NCA antibodies capable of enhancing efficacy of other anticancer treatments by increasing the differentiation status of a tumor and by enhancing the bystander effect. At page 7 (lines 20-27), the specification describes anti-CEA/NCA antibodies capable of restoring anoikis/apoptosis to levels of non-malignant or normal cells to thereby increase the efficacy of all other cytotoxic chemotherapeutic drugs that kill cells by a mechanism that depends upon apoptosis. However, the originally filed specification does not appear to describe anti-CEA/NCA antibodies *capable of disrupting a CEA/NCA interaction* involving a N-terminal domain of CEA/NCA.

Claim 28 recites, "at least one". Applicant added claim 28 by the amendment filed April 2, 2004 without stating wherein the specification, including the claims, as originally filed, written support for the claim language can be found. The specification, including the claims, as originally filed, does not appear to provide adequate written support for the instant claim language, since it does not appear that the specification describes an inhibition by an antibody of an interaction between one or any combination of the recited CEA/NCA subdomains, limited to or including the subdomain of SEQ ID NO: 1. Therefore, the recitation appears to introduce new matter.

Claim 29 recites, "with a cytotoxic agent". Applicant added claim 29 by the amendment filed April 2, 2004 without stating wherein the specification, including the claims, as originally filed, written support for the claim language can be found. It does not appear that the originally filed specification, including the claims, provides any degree of written support for the recitation in the instant claim, which would reasonably convey to the skilled artisan that Applicant had, or even had contemplated the claimed invention, because the combination is not described.

These issues might be resolved if Applicant were to point to particular disclosures in the specification, as originally filed, which are believed to provide the necessary written support for the instant claim language.

18. Claims 25 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

Hampton et al. (*Oncogene* **21**: 7817-7823, 2002), for example, teaches the gene encoding CEA is alternatively spliced, such that the gene encodes different isoforms of CEA. Furthermore, Kuroki et al. (*J. Biol. Chem.* **266**: 11810-11817, 1991), for example, teaches "NCA" defines at least 12 different species of molecule.

Rojas et al. (*Cell Growth Differ.* **7**: 655-662, 1996) (of record) teaches even closely related members of the CEA gene family have radically different functions, including the properties of adhesion; see entire document, particularly the abstract. More generally, Skolnick et al. (*Trends in Biotechnology* **18**: 34-39, 2000) discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept an assertion, which is based only upon an observed similarity in amino acid sequence, that any CEA or NCA isoform, or any protein comprising SEQ ID NO: 1 would similarly be involved in inhibiting anoikis or terminal differentiation, or in distorting tissue architecture.

Accordingly, the claims are drawn to a genus of CEA and NCA species, which vary in structure and function. However, Applicant's instant disclosure of the claimed

Art Unit: 1642

invention does not adequately describe either of the proteins in sufficient detail to allow the skilled artisan to instantly envision, recognize, or distinguish at least a substantial number of the species of CEA and NCA that are encompassed by the claims. Moreover, Applicant has not described any one species of CEA or NCA by disclosing either the amino acid sequence of the protein or the nucleotide sequence of the gene encoding the protein.

MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In deciding *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the Court states, “[a]n adequate written description of a DNA...’requires a precise definition, such as by structure, formula, chemical name, or physical properties’, not a mere wish or plan for obtaining the claimed chemical invention”. As the claims are particularly directed to proteins encoded by DNA, it follows that an adequate written description of the proteins requires a precise

definition, such as by a disclosure of at least a representative number of the amino acids sequences of those proteins.

*The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (*Id.* at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Because the specification does not describe CEA or NCA in a manner that the skilled artisan could immediately recognize the proteins to which the claims are directed, the written description requirement set forth under 35 USC § 112, first paragraph, would not be met by the instant disclosure.

19. Claims 25 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 1 (lines 5-9), the specification discloses the claimed invention can be used to treat cancer. However, the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to use the claimed invention to treat cancer without having the need to perform additional, undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The relevant art is characterized as highly complex and unpredictable. Considering the nature of the invention and the breadth of the claims, it appears that the amount of guidance, direction, and exemplification provided by Applicant's disclosure is not reasonably commensurate in scope with the claims. Thus, the state of the art, now and at as of the earliest filing date sought by Applicant, is such that, in the absence of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, the skilled artisan could not use the claimed invention successfully without having to perform an undue amount of additional experimentation, which extends beyond the realm of routine experimentation.

Regarding the possibility that the claimed invention might be used to treat cancer, Gura (*Science* 1997; **278**: 1041-1042), for example, teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for

Art Unit: 1642

chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Accordingly, the skilled artisan cannot predict whether or not the claimed invention can be used effectively to treat cancer; and since the specification fails to exemplify the use of the claimed invention, the skilled artisan could not use the claimed invention without having the need to first perform an undue amount of additional experimentation to determine which, if any types of cancer might be successfully treated using the claimed invention.

In addition, "CEA" and "NCA" are different proteins having unique structures and functions; see, for example, Neumaier et al. (*J. Biol. Chem.* **263**: 3202-3207, 1988) and Barnett et al. (*Genomics* **3**: 59-66, 1988). The family of "CEA"- and "NCA"-related proteins comprises a multitude of members having varying structure and function. Thus, as the claims are apparently drawn to a method comprising incubating tumor cells with an antibody that binds a member of a genus of CEA and NCA species of protein, it is aptly noted that Rojas et al. (*Cell Growth Differ.* **7**: 655-662, 1996) (of record) teaches even closely related members of the CEA gene family have radically different functions, including the properties of adhesion; see entire document, particularly the abstract. For example, Rojas et al. teaches that some proteins encoded by the members of the larger gene family mediate adhesion by a mechanism that is reversibly  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  dependent, temperature dependent, and inhibited by ATP, whereas other members mediate adhesion by a mechanism that is opposed in every one of these aspects (abstract). Due to the varying functions of proteins designated "CEA" and "NCA", the skilled artisan could not practice the claimed invention without the need to first perform an undue amount of additional experimentation to determine if the protein to which the antibody binds is involved in inhibiting terminal differentiation and anoikis of tumor cells

expressing the protein, and whether or not the antibody is capable of interfering with these functions in a manner that might be useful in treating cancer.

At page 16 (lines 26-30), for example, the specification suggests that interference of CEA-CEA or NCA-NCA intermolecular adhesion of tumor cells and other cells, which facilitates tumorigenesis, might provide a means to treat cancer. However, Jessup et al. (*Clin. Exp. Metastasis* 17: 481-488, 1999) teaches CEA expression does not effect adhesion of tumor cells to Kupffer cells and hepatic sinusoidal endothelial cells (abstract). Thus, contrary to Applicant's suggestion, at least in the case of liver metastasis, Jessup et al. concludes that CEA enhances liver colonization through another mechanism, possibly one that involves modulation of hepatic response to tumor cell implantation, rather than by CEA-mediated adhesion; see entire document, particularly the abstract. In view of the differences in structure and function of NCA, as compared to CEA, it follows that the skilled artisan cannot predict whether NCA-NCA intermolecular adhesion is involved in metastasis. Thus, in view of the teachings of Jessup et al., the skilled artisan could not use the claimed invention to treat cancer without the need to first perform an undue amount of additional experimentation to determine if an anti-CEA/NCA antibody can be used to inhibit tumorigenesis.

Furthermore, Rojas et al. (cited *supra*) teaches CEA and NCA are expressed only in primates, and notably not in rodents (abstract); therefore, determining whether or not the claimed invention can be used to treat cancer might necessarily involve the employment of xenograft animal models in which human tumor cells have been transplanted into an experimental animal. Because Gura teaches the results acquired using such animal models cannot be extrapolated to reliably predict the outcome of treating a human in the same manner, it is apparent that absent exemplification of the claimed invention, an undue amount of additional experimentation would have to be performed before the skilled artisan could use the claimed invention to treat cancer in humans.

As evidenced by the teachings of the references cited above to address the level of skill in the art and the state of the art, now and as of the earliest filing date sought by Applicant in the instant application, the art is characterized by a high level of complexity,

Art Unit: 1642

as well as unpredictability. Upon considering the nature of the invention and the breadth of the claims, it appears that the amount of guidance, direction, and exemplification set forth by Applicant is not reasonably commensurate in scope with the claims. Therefore, although the relative skill of those in the art is high, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation, that is, beyond the realm of routine experimentation, would have to be performed before the claimed invention, commensurate in scope with the claims, could be made and used.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

20. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 25 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25 and 28-30 are vague and indefinite because claims 25 and 28 recite "CEA/NCA". The recitations renders the claims vague and indefinite because it cannot be determined if the term "CEA/NCA" designates a single protein, which can be, or has been designated by both "CEA" and "NCA", or if the term "CEA/NCA" designates two different proteins, namely "CEA" and "NCA", or if perhaps the members of the greater family of "CEA"- and "NCA"-related proteins. Regarding the antibody to which the claims are directed, it cannot be determined if the antibody binds either "CEA" or "NCA", both "CEA" and "NCA", or to any or all of proteins of the greater family of "CEA"- and "NCA"-related proteins. Moreover, as there are more than one protein designated

"CEA" and "NCA" (see the written description rejection above), the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter that Applicant refers to by use of these designations, and therefore would not be reasonably apprised of the subject matter that Applicant regards as the invention. Moreover, the use of laboratory designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. Amendment of the claims to include the amino acid sequence of the polypeptide by reference to a specific sequence identification number of an amino acid sequence set forth in the Sequence Listing can obviate this rejection, because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide; however, Applicant is cautioned against introducing new matter by amendment.

### ***Claim Rejections - 35 USC § 102***

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 25, 28, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan et al. (*J. Biol. Chem.* **272**: 27902-27907, 1997).

The claims are drawn to a method for relieving a CEA/NCA-imposed inhibition of differentiation and/or apoptosis comprising an incubation of primary or secondary tumor cells with an anti-CEA/NCA monoclonal antibody that disrupts an interaction involving a CEA/NCA subdomain having SEQ ID NO: 1.

Yan et al. teaches incubating tumor cells in the presence of Fab' fragments of an anti-CEA monoclonal antibody; see entire document, particularly page 27905, column 2. Yan et al. discloses that the antibody inhibits adhesion, preventing the formation of cell aggregates (page 27905, column 2).

Art Unit: 1642

Although Yan et al. does not expressly teach that the antibody disrupts an interaction involving a CEA/NCA subdomain having SEQ ID NO: 1, because the antibody inhibits cell aggregation, the antibody inhibits adhesion mediated by CEA. Because the antibody inhibits CEA-mediated adhesion, the antibody inhibits interactions involving any subdomain of CEA, including the subdomain of SEQ ID NO: 1, through which CEA would otherwise adhere to another molecule. For this reason, absent a showing of any difference, the method of the prior art is deemed the same as the claimed method.

24. Claims 25, 28, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Jessup et al. (*Int. J. Cancer* **55**: 262-268, 1993).

The claims are drawn to a method for relieving a CEA/NCA-imposed inhibition of differentiation and/or apoptosis comprising an incubation of primary or secondary tumor cells with an anti-CEA/NCA monoclonal antibody that disrupts an interaction involving a CEA/NCA subdomain having SEQ ID NO: 1.

Jessup et al. teaches incubating tumor cells in the presence of an anti-CEA monoclonal antibody that cross-reacts with NCA; see entire document, particularly the abstract. Jessup et al. discloses that the antibody inhibits adhesion (abstract). Jessup et al. teaches the antibody bind to epitopes in the N-terminus of CEA and NCA (page 263, column 1). Jessup et al. teaches the epitope in the N-terminus of the proteins is involved in mediating an interaction that facilitates adhesion; see, e.g., page 267, column 2.

Because the antibody of Jessup et al. binds to an epitope in CEA and NCA and inhibits adhesion by disrupting an interaction involving the N-terminus of CEA and NCA, which comprises the subdomain of SEQ ID NO: 1, the antibody of Jessup et al. appears to be the same as the antibody to which the claims are directed. Accordingly, absent a showing of any difference, the method of the prior art is deemed the same as the claimed method.

Art Unit: 1642

**Conclusion**

25. No claims are allowed.

26. The art made of record and not relied upon is considered pertinent to Applicant's disclosure. Zhou et al. (1993) (of record) teaches an anti-CEA/NCA antibody that effects CEA-mediated adhesion. Levin et al. teaches adhesion of CEA-bearing colorectal cancer cells. Krop-Watorek et al. reviews the CEA antigen as an adhesion molecule. Taheri et al. (2000 and 2003) teaches subdomains of CEA required for intracellular adhesion and anti-CEA/NCA antibodies capable of inhibiting intercellular adhesion and releasing CEA-associated block of myogenic terminal differentiation.


27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.  
Examiner  
Art Unit 1642

slr  
July 16, 2004

  
SUPERVISORY PATENT  
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